## REMARKS

Claims 22-25, 28, 29, 33-40, 43, 46, 47, 59, 62, 64, 87-89, 96, 101, 106, 108-111, 116, and 117 are pending. Claims 46 and 117 have been amended. The amendments to the claims do not introduce new subject matter and were made to more clearly define the claimed subject matter. A complete set of the pending (examined and withdrawn) claims is provided for the Examiner's convenience.

Attached hereto is a "VERSION WITH MARKINGS TO SHOW CHANGES MADE" to detail the amendments made to the claims.

*Interview*

The applicants thank the Examiner for conducting a telephonic interview with the applicants' representatives, John J. Gresens and Mark E. Deffner, on April 23, 2003. In summary, the parties discussed the limitation regarding specificity of the claimed method and how it distinguishes the invention over the prior art and is not the result of mere optimization. The parties further discussed the reasons for the new matter rejection and specific parts of the specification that support the limitations at issue.

*35 U.S.C. § 112 – Second Paragraph*

Claims 46-47, 106, and 117 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The applicants respectfully traverse this rejection.

While not conceding the correctness of the examiner's position, the applicants have amended claims 46 and 117 obviating this rejection. Accordingly, the applicants respectfully request that this rejection be withdrawn.

*35 U.S.C. § 103*

Widder, Connelly, and Abram

Claims 22-25, 28-29, 33, 36-38, 59, 62, 64, 101, and 108-111 are rejected under 35 USC §103(a) over *Widder* et al. (EP 016,552) in view of *Connelly* et al. (U.S. Patent No. 5,422,277) in further view of *Abram* et al. (U.S. Patent No. 4,497,900). Applicants traverse this rejection and respectfully request reconsideration.

*Widder* discloses a method for coarse separation of blood cells through use of microspheres having protein A associated with the outer surfaces thereof. However, *Widder* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Connelly* does not overcome the deficiencies of *Widder*, as *Connelly* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Connelly* merely directs the reader to a cell fixative composition for fixing the internal components of a cell without disrupting the cell surface components.

*Abram* does not cure the deficiencies of *Widder* and *Connelly* and is further removed from the concept of the claimed invention. Instead of detecting a membrane structure on an intact, live target cell, the antibodies described by *Abram* are directed to antigens from lysed bacteria that have been absorbed onto plastic beads. Moreover, *Abram* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. Thus, the combination of *Widder*, *Connelly*, and *Abram* fails to teach all the elements of the claimed invention.

The office action states that the sensitivity levels claimed appear to be achieved by optimization procedures. However, the applicants assert that such a large difference in sensitivity as taught by the prior art in comparison to the sensitivity as claimed in the present invention cannot be a matter of mere optimization.

*Widder* discloses, for example, at the last line of page 11, that the non-specific binding is somewhat less than 10 percent. Based on this disclosed level of non-specific binding, one could not expect a sensitivity level of greater than 1 target cell per 10 total cells following the method of *Widder*. In contrast the present invention discloses and claims much greater sensitivity levels. Presently, the claims recite a sensitivity level of 1 target cell per 100 or more total cells. This represents a sensitivity that is at least one full order of magnitude greater. Further, the method of the present invention is capable of specificities even higher. A sensitivity of 1 target cell per $10^4$ total cells is disclosed on lines 13-14 of the first paragraph on page 21. In view of the extreme differences in sensitivities between the prior art and the disclosed method, the applicants assert that such a difference cannot be achieved by mere optimization procedures.

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Review of the case cited by the office action supports the view that the difference in sensitivities is not mere optimization. The office action cited Application of Aller, 220 F.2d 454, 456 (C.C.P.A. 1955) for the proposition that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." However, the present case is easily distinguishable from Aller. In Aller the only difference between the claimed invention and a SINGLE prior art reference was lower temperatures and higher sulphuric acid concentrations than in the reference. The court found that "the improvement is but a few percentage points different from the results reported by the reference." *Id.* at 457. In contrast, the difference in the sensitivities between the prior art and that claimed in the present case are a full order of magnitude different, or 1000%.

Therefore, *Widder, Connelly,* and *Abram,* taken alone or in combination, do not teach all the elements of the claimed invention. Applicants respectfully request this rejection be withdrawn.


Widder, Connelly, Abram, and Forrest

Claims 46-47, and 106 are rejected under 35 USC §103(a) over *Widder* et al. in view of *Connelly* et al., in further view of *Abram* et al. and *Forrest* et al. Applicants traverse this rejection and respectfully request reconsideration.

The Examiner maintains that it would have been obvious to incorporate the antibodies, buffers, beads, and reagents in the methods of *Widder, Connelly* and *Abram* into a test kit such as that taught by *Forrest* because test kits are conventional and well known in the art.

*Forrest* does not overcome the deficiencies of *Widder, Connelly* and *Abram.* As discussed above, the combination of *Widder, Connelly* and *Abram* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Forrest* does not teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. As such, a combination of *Widder, Connelly, Abram* and *Forrest* would not achieve the instant invention. Applicants respectfully request this rejection be withdrawn.

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Widder, Connelly, Abram, Kemmner, and Holmes

Claims 34-35, 39-40, 43, 87-89, 96 and 116 are rejected under 35 USC §103(a) over *Widder* et al. in view of *Connelly* et al., and further in view of *Abram* et al., *Kemmer* et al. and *Holmes* et al. Applicants traverse this rejection and respectfully request reconsideration.

*Kemmner* and *Holmes* do not overcome the deficiencies of *Widder, Connelly* and *Abram*. As discussed above, the combination of *Widder, Connelly* and *Abram* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. *Kemmner* is cited for teaching isolation of tumor cells using magnetic beads coated with monoclonal antibodies. *Holmes* is cited for teaching a method of separating hematopoietic progenitor cells from a mixed population using microbeads coated with antibodies. However, *Kemmner* teaches their method as detecting only 40% of target cells present at a concentration of 73% of total cells (see page 199, second column). *Kemmner* teaches that steric hindrance and resulting reduced accessibility of epitopes for binding the antibody-coated beads, could be responsible for the reduced level of detection as opposed to the better results obtained by immunofluorescent assay on frozen tissue sections. Thus, *Kemmner* fails to teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells.

*Holmes* is directed to separating blood cells from a blood or bone marrow sample, which is specifically excluded from the instant claims. Thus, *Holmes* cannot be seen to provide any guidance or motivation for modifying any of the previously described prior art to achieve the instant invention.

As such, the combination of *Widder, Connelly, Abram, Kemmner,* and *Holmes* fails to achieve the instant invention. Applicants respectfully request this rejection be withdrawn.

Widder, Connelly, Abram, Kemmner, and Forrest

Claim 117 is rejected under 35 USC §103(a) over *Widder* et al. in view of *Connelly* et al., in further view of *Abram* et al., and in further view of *Kemmner* et al. and *Forrest* et al. Applicants traverse this rejection and respectfully request reconsideration.

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The Examiner maintains that it would have been obvious to incorporate the antibodies, buffers, beads, and reagents in the methods of *Widder, Connelly, Abram,* and *Kemmner* into a test kit arrangement such as that taught by *Forrest* because test kits are conventional and well known in the art.

*Forrest* does not overcome the deficiencies of *Widder, Connelly, Abram* and *Kemmner.* As discussed above, *Forrest* does not teach detecting a specific target cell at a sensitivity of one target cell per 100 or more total cells. As such, a combination of *Widder, Connelly, Abram, Kemmner* and *Forrest* would not achieve the instant invention. Applicants respectfully request this rejection be withdrawn.

### 35 U.S.C. § 112 – First Paragraph

Claims 22-25, 28-29, 33-40, 43, 59, 62, 64, 87-89, 96, 101, 108-111, 116, and 117 are rejected under 35 U.S.C. § 112, first paragraph, as not described in the specification. Specifically, the office action stated that the phrase "detecting a specific living target cell in a cell suspension of mixed cell population, or in a cell suspension prepared from a solid tissue, at a sensitivity of one target cell per 100 or more total cells" is not supported in the specification. The applicants respectfully traverse this rejection.

Support for the sensitivity limitation of one target cell per 100 or more total cells is contained in the specification. The applicants draw the examiner's attention to Example 10 at page 22 of the specification where it is disclosed that tumor cells were detected using the method of the invention wherein the tumor cells comprised between $0.1 - 1$ % of cells in the sample. This example provides support for the limitation of a sensitivity of one target cell per 100 or more total cells. The examiner's attention is further drawn to Example 8 at page 20 of the specification where it is disclosed that human breast carcinoma cells were detected at a sensitivity of one target-cell per $10^4$ nucleated cells. This example also provides support for the limitation of a sensitivity of one target cell per 100 or more total cells. Finally, the examiner's attention is drawn to the paragraph beginning on line 8 of page 8. Here it is disclosed that the method of invention can be used to detect target cells which represent a very low fraction of the total number of cells ($<= 1$%). For at least these reasons the applicants assert that the

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limitation of one target cell per 100 or more total cells is clearly supported by the specification.

Support for the limitation of the cells being live cells is also clearly contained in the specification. The applicants draw the examiner's attention to the third paragraph on page 3 of the specification where it is disclosed that "the present method can be used for isolation of cells for biochemical, biological and immunological examination, and for studying of specific genes at the nucleotide or protein level, *in addition to culturing the cells*, without the need for cleaving the cell-particles complex." (emphasis added) The applicants submit that this clearly contemplates live cells because otherwise it would not be possible to culture the target cells after their isolation. Moreover, the method of the present invention clearly contemplates live cells because it is disclosed in the third paragraph of page 11 that the method can be used without fixatives such as formaldehyde or alcohols.

In sum, the phrase "detecting a specific living target cell in a cell suspension of mixed cell population, or in a cell suspension prepared from a solid tissue, at a sensitivity of one target cell per 100 or more total cells" is clearly supported in the specification and the applicants respectfully request that this rejection be withdrawn.


In view of the remarks presented herein, Applicants respectfully submit that the claims are in condition for allowance. Notification to that effect is earnestly solicited. If prosecution of this case could be facilitated by a telephonic interview, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

### In the Claims:

Please amend claims 46 and 117 as follows:

46.     (Five Times Amended) A kit for performing the method of claim 22, the kit comprising:

   a.     a first antibody, wherein said first antibody is a specific monoclonal antibody or antibody fragment directed against a second antibody or antibody fragment, said first antibody [effective for] coating a paramagnetic particle or bead without removing its antigen-binding ability;

   b.     a paramagnetic particle or bead; and

   c.     the second antibody, wherein said second antibody is a specific monoclonal antibody or antibody fragment directed against an antigen or a receptor within or on the target cell;

   wherein said second antibody or antibody fragment is conjugated to a detectable label.

117.     (Twice Amended) A kit for performing the method of claim 22, the kit comprising:

   a.     a first antibody, wherein said first antibody is a specific monoclonal antibody or antibody fragment directed against a second antibody or antibody fragment, said first antibody [effective for] coating a paramagnetic particle or bead without removing its antigen-binding ability;

   b.     a paramagnetic particle or bead; and

   c.     the second antibody, wherein said second antibody is a specific monoclonal antibody or antibody fragment directed against an antigen or a receptor within or on the target cell, wherein the second antibody or antibody fragment is directed against fibronectin receptor, $\beta$-integrin, vitronectin receptor, $\alpha\gamma\beta3$-integrin. P-seletin including GMP-140, CD44-variants, N-CAM including CD-56, E-cadherin, Le$^y$, carcinoembryonic antigen or CEA, EGF receptor, c-erbB-2 including HER2, transferin

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receptor, TNF-receptor, high molecular weight antigen, p95-100, sarcoma antigens including TP-1 and TP-3 epitope, Mv 200kD, Mv160kD, MOC-31 epitope including cluster 2 epithelial antigen, MUC-1 antigen including DF3-epitope and gp290kD, prostate high molecular antigen, TAG 72, bladder carcinoma antigen, Mv 48kD colorectal carcinoma antigen, lung carcinoma antigen Mv 350-420kD, Mel-14 epitope, $\beta_2$-microglobulin, Apo-1 epitope, or pan-human cell antigen;

wherein said second antibody or antibody fragment is conjugated to a detectable label.

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